

## **REMARKS**

### **Amendments**

Claims 33-46 were examined and stand rejected. Claim 36-37 have been canceled, and claims 44 and 46 have been amended.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Support for the amendments to the claims can be found throughout the specification, at, for example, page 47, lines 27-30, page 50, lines 10-14 and in Figure 3 as filed. As such, no new matter has been added.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Furthermore, the amendments are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

### **Rejection under 35 U.S.C. § 101**

The Examiner has rejected claims 33-46 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either an asserted utility which is specific and substantial, or a well established utility. Applicant respectfully traverses this rejection.

The Examiner has based the rejection on the alleged lack of a statistically significant difference between the prepulse inhibition observed in the claimed homozygous mice and wild-type mice. This conclusion is based upon error bars in Figure 3 of the prepulse inhibition values for wild-type mice, which the Examiner states “extend to and include the mean prepulse inhibition values for the transgenic knockout mouse”. Applicant disclosed in the specification (at page 51, lines 29-31) that the prepulse inhibition observed for the homozygous mutant mice as compared to wild-type control mice was significantly increased. Furthermore, Applicant is not aware of any standard of statistical significance of a phenotype required for the establishment of patentability (utility) of a transgenic mouse. Applicant notes that the presence of overlapping error bars does not necessarily establish or support a lack of statistical significance, as asserted by the Examiner.

In order to address the Examiner's concerns regarding statistical significance of the data displayed in Figure 3, Applicant will be submitting a declaration under 37 C.F.R. § 1.132. In the forthcoming declaration, the data used to create the graph illustrated in Figure 3 is presented. This data will show the prepulse inhibition values observed for each individual mouse tested, the average for the homozygous mice, the average for the wild-type control mice, and the results of tests relied on to determine statistical significance. As the originally filed specification stated a significant difference in prepulse inhibition between the two groups, and it is clear that Figure 3 was based upon the data presented in the Declaration, this data is supported by the originally filed application. The data is being presented merely to address the allegation by the Examiner that the difference in prepulse inhibition between the two groups is not statistically significant.

The utility rejection is further based upon Applicant's disclosure and the state of the art relating to prepulse inhibition (PPI), which indicates that PPI can be affected by negative affective states, such as fear or stress, and that the increased PPI phenotype is "opposite" to a characteristic observed in (human) schizophrenic patients. Applicant submits that these issues do not apply to the utility of the claimed transgenic mouse. With respect to negative affective states, both homozygous knockout and wild-type control mice would be exposed to the same affective states or factors. Therefore, if the increased PPI phenotype had been a result of a negative affective state such as fear or stress, this affect would be observed in both the homozygous knockout and wild-type control mice. However, this is not the case, in that only the homozygous mice exhibit increased PPI. Regarding the increased PPI being opposite to a characteristic observed in schizophrenic patients, Applicant contends that the transgenic mouse represents the ultimate model of antagonism of the target BSMAP gene. As described in Geyer (2002, *Mol. Psychiatry* Vol. 7, pages 1039-1053), mutant knockout mice with single gene disruptions represent a powerful tool to study sensorimotor gating, and to identify and characterize putative and known therapeutic agents capable of affecting prepulse inhibition (see page 1040-1041, particularly the paragraph bridging columns 1 and 2 on page 1041). The Geyer reference describes using mutant mice such as the claimed transgenic mouse in various stages of drug discovery to identify potential targets involved in sensorimotor gating or PPI, to optimize a potential target, such as the BSMAP gene, or to determine or confirm the mechanism of action of therapeutic agents used in the treatment of sensorimotor gating related diseases, such as schizophrenia. Each of these uses applies to the claimed mouse.

The Examiner has also based the rejection on the association between prepulse inhibition deficits and several disorders distinct from schizophrenia, such as schizotypal personality disorder, Huntington's disease, and DiGeorge/Velocardiofacial syndrome. However, the Applicant contends that the utility of the claimed mouse relates to the prepulse inhibition phenotype, and that the evidence supporting a link between PPI deficits and multiple human disorders only supports the value of the transgenic mouse in discovering the role of the BSMAP gene in such disorders and developing treatments for them by modulating PPI.

The Examiner's utility rejection is further based on the lack evidence regarding the physiological role of the BSMAP gene, as well as the lack of a single gene or genes that have been confirmed as a "schizophrenia genes." Applicant disagrees with this conclusion, in that Applicant's disclosure provides evidence of a role for the BSMAP gene in sensorimotor gating, and particularly in prepulse inhibition. This is credible to the skilled artisan in light of the homology between the mouse and human genomes, and the general acceptance that gene function in the mouse is related to and representative of that of humans. Furthermore, regarding the alleged lack of a "schizophrenia gene," Applicant argues that this is not relevant to the utility of the claimed transgenic mouse. Applicant contends that for the asserted utility of screening for agents that affect or modulate a phenotype, such as prepulse inhibition, the transgenic mouse need only exhibit the phenotype. A potential therapeutic agent will usually only target one gene or gene product, regardless of whether the symptom or disorder is associated with multiple genes or whether no genes have been identified or linked to the symptom or disorder.

Applicant submits that the arguments set forth above, especially in light of the Declaration submitted concurrently herewith, overcome each issue raised in the rejection under 35 U.S.C. § 101, and requests reconsideration and withdrawal of the rejection. Applicant contends that the pending claims, which relate to a transgenic mouse whose genome comprises a disruption in the mouse BSMAP gene, which exhibits increased prepulse inhibition relative to a wild-type mouse, to methods of making and using the mouse, to cells derived from the mouse, and to targeting constructs and methods of producing targeting constructs used to produce the mouse, are supported by an asserted specific and substantial utility.

**Rejection under 35 U.S.C. § 112, first paragraph - Enablement**

The Examiner has rejected claims 33-46 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

In one aspect, the Examiner has alleged that one skilled in the art would not know how to use the claimed invention as of the filing date because it is allegedly not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above. Specifically, this aspect of the rejection relates to the issues regarding statistical significance of the data in Figure 3, and the lack of information regarding the role of the BSMAP gene and schizophrenia genes in general. Applicant submits that this aspect of the enablement rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant in light of the arguments presented above (in response to the utility rejection under 35 U.S.C. § 101), and the forthcoming declaration under 37 C.F.R. § 1.132. As noted above, the pending claims are supported by a specific and substantial asserted utility and a well established utility.

In another aspect of this rejection, the Examiner asserts that it is not known how one can use a transgenic mouse comprising a heterologous (heterozygous?) disruption of the BSMAP gene or a cell without a phenotype distinguishable from a wild-type mouse. This aspect of the rejection is based on the unpredictability of phenotypes in transgenic mice, in light of the scope of the claims. Applicant submits that the cancellation of claims 36-37 and amendment of claim 44, drawn to heterozygous mice or cells without a phenotype, overcomes this issue. Each of the pending claims recite a phenotype resulting from disruption of the BSMAP gene which is supported by the originally filed specification.

Applicant submits that one skilled in the art would be able to make and use the invention as recited in claims 33-35 and 38-46. Applicant respectfully requests withdrawal of the rejection.

**Rejection under 35 U.S.C. § 112, second paragraph**

The Examiner rejected claim 46 under 35 U.S.C. § 112, second paragraph, for being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant respectfully traverses this rejection.

Specifically, the Examiner asserts that the claim is indefinite because there is no connection between the step of determining whether the potential therapeutic agent modulates prepulse inhibition in the transgenic mouse and modulation of seizure susceptibility. Claim 46 has been amended to recite modulation of prepulse inhibition and remove reference to seizure

susceptibility. Therefore the rejection is no longer relevant, and Applicant respectfully requests withdrawal of the rejection.

In light of the amendments to the claims and remarks set forth above, it is believed that the claims are currently in condition for allowance. Notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-227.

Respectfully submitted,

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Kelly L. Quast

Kelly L. Quast, Reg. No. 52,141

Deltagen, Inc.  
1031 Bing Street  
San Carlos, CA 94070  
(650) 569-5100